REMARKS

Reconsideration is respectfully requested.

Claims 1, 5, 19, 20, and 22 have been amended. Claims 4, 8, 9, and 23 have been cancelled. Claims 2-3, 6-7, 10-18, and 21, and 24-27 are reiterated. Claims 28-32 have been added. Claims 1-3 and 5-7, 10-22, and 24-32 are pending.

Claim 4 has been cancelled in favor of claims 22-27 and 32, also directed to kits.

Claims 8, 9, and 23 have been replaced by claims 30, 31, and 32 to overcome the Examiner's objection to the order of the claims, as discussed below. Claims 30, 31, and 32 are identical to cancelled claims 8, 9, and 23, respectively.

Drawings

The Examiner has objected to the drawings. The Notice of Draftsperson's Patent Drawing Review states that the lines, numbers, and reference characters are of poor quality in all the drawings.

Applicants have submitted replacement sheets of drawings labeled "Replacement Sheet." The replacement sheets of drawings have well characterized lines, numbers, and letters. Since Applicants have corrected the drawings to comply with the Examiner's objection, Applicants respectfully request that this ground for objection be withdrawn.

Specification

Title

The Examiner has objected to the title as not descriptive. The Examiner requires a new title that clearly indicates the invention to which claims are directed.

Applicants have changed the Title to "Method and Kit for a Nuclear-Run On Assay." Applicant asserts that the new title is descriptive and that this ground for objection is therefore moot. Applicant respectfully requests that it be withdrawn.

Trademarks

The Examiner notes that the patent application includes a number of trademarked products. Applicants note that the Examiner has not objected to the Specification over reference to trademarked products.

Applicants agree that the trademarks should be capitalized wherever they appear in the Specification. Applicants also agree that the proprietary nature of the marks will be respected and that every effort will be made to prevent their use in any manner that might adversely affect their validity as trademarks.

Incorporation by Reference

Applicants have incorporated U.S. Provisional Application No. 60/316,308 by reference in its entirety. Since the entire provisional patent application is pertinent to the present patent application, Applicants identified the entirety of the patent application for incorporation by reference.

In addition, Applicants have disclosed numerous references citing compositions and techniques that that explain known and/or conventional compounds used in the claimed methods. Applicants are not required to disclose in the specification what is well known or conventional in detail. See *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F. 2d at 1384, 231 USPQ at 94. In the present case, Applicants provide an extensive discussion of well known, conventional compounds and methods used in the methods of the presently claimed invention. Applicants have cited numerous references in the patent application illustrating various aspects that were well known and conventional at the time of filing.

Claim Objections

The Examiner objects to the claims, arguing that a claim that depends from a dependent claim should not be separated by any claim that does not also depend from the dependent claim. The Examiner states that in the present case, dependent claim 5 is separated from independent claim 1 by dependent claim 4, dependent claims 10-21 are separated from independent claim 6 by dependent claims 8 and 9, and dependent claims 24-27 are separated from independent claim 22 by independent claim 23.

Applicants can find no support for this ground for objection in MPEP 608.01(n). However, to expedite prosecution, Applicants have amended the claims to put the claims in the correct order by subject matter. Specifically, Applicants have cancelled claim 4. Applicants have replaced claims 8-9 with identical claims 30-31. Applicants have also replaced claim 23 and replaced it with claim 32. Claims 30, 31, and 32 are identical to claims 8, 9, and 23, respectively.

This ground for objection is now moot. Applicants respectfully request that it be withdrawn.

35 U.S.C §112, first paragraph, enablement

The Examiner has rejected claims 1-3 and 5 under 35 U.S.C §112, first paragraph for failing to comply with the enablement requirement.

The Examiner argues that it is impossible to achieve magnetic separation of the RNA transcripts that have already been cleaved from the iron particles. Applicants have amended claim 1 to require that cleavage from the iron fragments occurs after "magnetic separation."

This rejection is therefore moot, and Applicants respectfully request that it be withdrawn.

35 U.S.C §112, first paragraph, written description

The Examiner has rejected claims 22-27 for failing to comply with the written description requirement.

Claims 22-27

Claim 22 is directed to "a kit for determining the rate of transcription of a transcriptional unit in one or more cells, said kit comprising: enzymes, buffers, and diluents for obtaining nucleic acids; biotin-labeled ribonucleotides, wherein said biotin-labeled ribonucleotides include a cleavable linker between said biotin and said ribonucleotide; enzymes, buffers, and diluents for transcription of nucleic acids; a solid matrix; enzymes, buffers, and diluents for isolating biotin-labeled molecules using said solid matrix; and enzymes, buffers, and diluents for real time polymerase chain reaction." Claims 24-27 depend from claim 22.

Claim 23 claims the compositions of claim 22, and further limits the matrix, "wherein the matrix includes a cleavable linker."

The Examiner's Rejection

The Examiner has rejected claims 22-27 as allegedly failing to comply with the written description requirement. The Examiner admits that the specification supports a variety of possible configurations, but alleges that the Specification "fails to provide an adequate written description of enzymes that are to be used when 'obtaining nucleic acids' from any source." The Examiner concludes that "while it may have been obvious to one of skill in the art at the time the invention was made to have selected various components and to have placed them in a kit, along with pertinent instructions, such an argument does not render moot the need for the disclosure to provide an adequate written description of the invention."

Applicant's Response

The written description requirement prevents an Applicant from obtaining patent protection for speculative inventions they did not have. As the Examiner noted, the requirements for a lack of a written description were articulated in *University of California v. Eli Lilly,* 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). In *Lilly*, the patent holder claimed, but failed to disclose, the sequence of human insulin. The *Lilly* court held that the disclosure of a single species of insulin (rat insulin) was not a sufficient written description of a genus of all vertebrate insulin. In addition, the patent holder in *Lilly* only disclosed the sequence of rat insulin, and not the sequence of human insulin, at the time the patent was filed.

The circumstances of the present application are completely different from those in *Lilly*. In *Lilly*, human insulin was unknown to the patent holder at the time of filing. In the present application, however, Applicants have disclosed numerous methods and compositions that may be used as parts of different components of the claimed kits. In *Lilly* the patentee did not know or disclose the genus of compounds at the time of filing. In the present application, Applicants have disclosed a number of methods and compounds that can be used in the present invention.

Further, Applicants are not required to disclose what is well known or conventional in detail. See *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F. 2d at 1384, 231 USPQ at 94. In the present case, Applicants claim enzymes, buffers and diluents that are well known and conventional. Furthermore, Applicants provide an extensive discussion of well known, conventional compounds and methods used in the methods of the presently claimed invention. Applicants have provided an extensive description, and cited numerous references, illustrating various aspects that were well known and conventional at the time of filing. These references are merely illustrative of many well known and conventional enzymes, buffers and diluents available to the person of ordinary skill.

Illustrative of the broad disclosure provided by Applicants, the Examiner is directed to page 14, line 30 through page 15, lines 1-11, where Applicants disclose the Polymerase Chain Reaction (PCR), and reference U.S. Patent 4,683,202 and 4,683,195, both issued to Mullis. Applicants disclose ligases, for example those used in the Ligase Chain Reaction (LCR) as

described in European Patent Application No. EP-A-320 308 (Backman et al.), Gap LCR and variations disclosed in WO 90/01069 and European Patent Application No. EP-A-439 182 (Backman et al.), British Patent No. GB 2,225,112A (Newton et al.) and International Patent Pub. No. WO 93/00447 (Birkenmeyer et al.), QB replicase, Strand Displacement Amplification (SDA) as described in European Patent Application Nos. EP-A-497 272 (Walker) and EP-A-500 224 (Walker et al.), self-sustained sequence replication (3SR), and Nucleic Acid Sequence-Based Amplification (NASBA). Applicants further describe the differences between PCR, LCR, and Gap LCR at page 15, lines 13-25. Applicants specifically disclose ligase enzymes at page 15, line 19. Applicants disclose Taq polymerase at page 25, lines 13-19 as an example of thermostable polymerases. Applicants also provide examples of enzymes, buffers, and diluents used to amplify the nucleic acids in Examples 12 through 18. Thus, both the disclosure and the references cited in the specifcation contain extensive discussion of numerous enzymes, buffers, and diluents. Furthermore, one of ordinary skill is readily aware of numerous commercially available enzymes, buffers and diluents. Such enzymes, buffers and diluents are well known and conventional One of skill in the art would therefore conclude that Applicants have possession of enzymes, buffers, and diluents, as claimed.

Enzymes, buffers and diluents for isolating biotin-labeled molecules using a solid matrix are well known and commercially available. Furthermore, the disclosure also provides an extensive written description of enzymes, buffers and diluents for isolating biotin-labeled molecules using a solid matrix. At page 20, the Specification discloses strepatvidin, avidin, and anti-biotin antibodies, all of which bind biotin. At page 27, lines 17-26, Applicants disclose a wide variety of solid matrices. At page 28, lines 1-8, Applicants disclose one method of isolating labeled RNA transcripts, using a solid matrix in detail. At page 29, lines 4-13, Applicants describe streptavidin in more detail, and at page 29 lines 14-17 Applicants disclose non-strepatividin proteins capable of binding biotin. Enzymes, buffers and diluents for isolating biotin-labeled molecules using a solid matrix are well known and conventional. Based on the wide variety of enzymes, buffers, and diluents available commercially including those disclosed herein, one of skill in the art would conclude that Applicants had possession of enzymes, buffers, and diluents for isolating biotin-labeled molecules using a solid matrix.

Applicants also provide an extensive description of buffers, reagents, and enzymes used in Real-Time-PCR (RT-PCR). RT-PCR is an established method of measuring kinetics of nucleotide reactions. Enzymes, diluents and buffers for RT-PCR are readily available commercially. Applicants provided multiple references in the previously submitted Information Disclosure Statement that discuss RT-PCR in detail (courtesy copies of which are provided herein). Specifically, Rolfe & Sewell, *J. Immunol. Methods*, 202 (1997) 143-151, discusses methods of measuring mRNA stability by RT-PCR, and Svanvik et al., *Anal. Biochem.* 287, 179-182 (2000) discusses using PNA probes to detect. These references provide support for Applicant's position that RT-PCR is known and conventional. Applicants also describe real-time analysis throughout the present application, for example, at page 16, line 23 through page 20, line 22. The description includes thermal cyclers (page 17, lines 1-3), methods of detecting fluorescent probes (page 17 line 10 through page 18, line 7), molecular beacons, probes, and fluorophores (page 18 line 19 through page 20, line 22). Applicants further describe fluorophores at page 26 lines 18-28. Applicants also provide examples illustrating RT-PCR. Example 14 provides an example of establishing RNA standard curves. Example 15 discloses an example of preparing nucleic acids to establishing standard curved. Example 16 teaches quantitative analysis of nascent RNA transcription levels by real-time PCR - target choice. Examples 17 and 18 each provide extensive discussion of RT-PCR and modified RT-PCR. Applicants have also provided numerous figures demonstrating how to determine transcription kinetics using RT-PCR. Figures 1-6 disclose RT-PCR curves, and show the calculated synthesis kinetics, including standard deviations. One of skill in art would conclude that Applicants had possession of the claimed invention.

Applicants have described in significant detail the components of the invention. These components are conventional and known and readily available in the art. The facts of the present Application are entirely different from those of *Lilly*. In *Lilly,* the applicant attempted to claim an undisclosed and unknown DNA sequence. The DNA sequence was not well known or conventional or available since it had not been isolated. In contrast, in the present invention, enzymes, buffers and diluents are well known and conventional as the they have been isolated and are commercially available. As such, *Lilly,* is simply not applicable to the present case.

Applicants therefore respectfully request that this ground for rejection be withdrawn.

35 U.S.C. §112, second paragraph

Claims 1, 2, 3, and 5-21

The Examiner has rejected claims 1, 2, 3, and 5-21 as being indefinite for failing to particularly point out or distinctly claim the invention. The Examiner argues that the claims omit essential steps amounting to a gap between claims. The Examiner argues that the omitted steps are steps that result in the actual determination of the rate of transcription of a transcriptional unit.

Applicants have not omitted any steps. The step of determining the rate of transcription is accomplished by "real-time PCR," which is an established, well know and conventional method of determining the kinetics of nucleotide polymerization. As noted above, Applicants provided multiple references in the Information Disclosure Statement that discuss RT-PCR in detail (courtesy copies of which accompany this response). Specifically, Rolfe & Sewell, *J. Immunol. Methods*, 202 (1997) 143-151, discusses methods of measuring mRNA stability by RT-PCR, and Svanvik et al., *Anal. Biochem.* 287, 179-182 (2000) discusses using PNA probes to detect. Further, Applicants have discussed real-time PCR extensively in the Specification. Applicants describe real-time PCR, for example, at page 16, line 23 through page 20, line 22. The description includes thermal cyclers (page 17, lines 1-3), methods of detecting fluorescent probes (page 17 line 10 through page 18, line 7), molecular beacons, probes, and fluorophores (page 18 line 19 through page 20, line 22). Applicants further describe fluorophores at page 26 lines 18-28. Applicants have also provided examples illustrating how to determine kinetics using RT-PCR. Example 14 provides an example of establishing RNA standard curves. Example 15 discloses an example of preparing nucleic acids to establish a standard curve. Example 16 teaches quantitative analysis of nascent RNA transcription levels by real-time PCR – target choice. Examples 17 and 18 each provide extensive discussion of RT-PCR and modified RT-PCR. Figures 1-6 disclose RT-PCR curves, and show the calculated

synthesis kinetics, including standard deviations. There is no missing step, since determining kinetics of polymerization is accomplished by RT-PCR.

This ground for rejection is therefore moot. Applicants respectfully request that it be withdrawn.

Claims 1, 4, 6, 8, 22, and 23

The Examiner has rejected claims 1, 4, 6, 8, 22, and 23 as indefinite for using the term "real time PCR." The Examiner argues that the term "real time" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree or scope of the claim.

Applicants respectfully traverse this rejection. The plain meaning of RT-PCR, as discussed above, is readily known to those of ordinary skill in the art. Applicants respectfully request that this ground for rejection be withdrawn.

Claims 6 and 18-20

The Examiner has rejected claims 6 and 18-20 as indefinite with respect to the term "exposing." The Examiner wonders whether "the cells need to be transfected with something or is it enough that it is in the same room state or country for there to be exposure."

Claim 6 does not include the claim limitation "exposing." Since the limitation is not found in claim 6, Applicants respectfully request that this ground for rejection be withdrawn.

Claim 18, and the claims that depend therefrom, are directed to "exposing a second portion of cells to one or more internal or external stimuli." "Exposing" has a readily understood plain meaning. One of skill in the art would readily understand the metes and bounds of "exposing" cells to stimuli.

The Examiner argues that one of skill in the art would somehow not be clear on whether "exposing" cells to a stimulus could extend to the cells being in the same room, state, or country as a

stimulus. It is clear to those of skill in the art that the metes and bounds of the plain meaning of the term "exposing" depend on the stimulus. For example, if one were exposing cells to stimuli by transfecting the cells with a compound, one of skill in the art would understand that the stimulus must be applied in the same room. If one were exposing cells to radiation, one of skill in the art would understand that the stimulus could be applied at a distance. Regardless, there is no question that the ordinary plain meaning of "exposing" cells to "one or more internal or external stimuli" is clear to one of ordinary skill in the art.

In light of the foregoing, Applicants respectfully request that this ground for rejection be withdrawn.

Claim 19

The Examiner has rejected claim 19, as indefinite. The Examiner alleges that the claim "is confusing as to how portions of cells are exposed to 'endogenous genes'."

Applicants have amended claim 19 to indicate that the stimuli "comprise at least a portion of the nucleic acid sequence of an endogenous gene." This includes the case in which a stimulus comprises a portion of a nucleic acid sequence capable of gene silencing. This amendment merely clarifies the present claim.

This ground for rejection is now moot. Applicants respectfully request that it be withdrawn.

Claim 20

The Examiner has rejected claim 20 for the limitation "trangene."

Applicants have amended claim 20 to be directed to "transgene." This ground for rejection is therefore moot. Applicants respectfully request that it be withdrawn.

Rejection 35 U.S.C. §102(b)

The Examiner has rejected claim 4 under 35 U.S.C. §102(b) over Burmer et al. (U.S. Patent No. 5,935,788).

Without admitting or acquiescing to the Examiner's rejection, Applicants have cancelled claim 4. This rejection is therefore moot. Applicants respectfully request that it be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. According, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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